

## **REMARKS**

Reconsideration of this application is respectfully requested in view of the following remarks.

### **I. Claim Status**

The Examiner has rejoined the photosensitizers and the prolactin enhancers recited in the claims and examined the full scope of claims 1-22.

Claim 20 has been cancelled, without prejudice or disclaimer.

Claims 23 and 24 have been added. Support for the claims is found in the specification at page 13, lines 24-25 and page 14, lines 16-18. By this Amendment, no new matter has been added to the application.

Upon entry of this Amendment, claims 1-19, and 21-24 are pending.

### **II. Double Patenting [sic] Objection**

Claim 20 stands objected to for being a substantial duplicate of claim 15. In response, claim 20 has been cancelled.

### **III. Ownership/Inventorship of U.S. Patents No. 5,792,748 and 6,071,914**

The Examiner has asked for clarification of the ownership and inventorship of U.S. Patents No. 5,792,748 ("the '748 patent") and 6,071,914 ("the '914 patent").

The '748 patent is assigned to The General Hospital Corporation ("Mass General") and The Board of Supervisors of Louisiana State University and Agricultural and Mechanical College ("LSU"). Anthony H. Cincotta and Albert H. Meier are joint inventors of the subject matter claimed in the '748 patent. The '914 patent is assigned to LSU and VeroScience, LLC. Anthony H. Cincotta and Albert H. Meier are joint inventors of the subject matter claimed in the '914 patent. The present application is assigned to Mass General and President and Fellows of Harvard College. Anthony H. Cincotta and Louis Cincotta are joint inventors of the claims pending in the present application.

**IV. Rejections for Obviousness-Type Double Patenting and Under 35 U.S.C. §103 over U.S. Patent No. 5,792,748, Werning, and Cincotta.**

Claims 1-3, 6, 10, 15, 20, 21 and 22 have been rejected under the judicially created doctrine of obviousness-type double patenting, as allegedly obvious over claims 3, 8, 13 and 19 of the '748 patent in view of Werning et al., *Arch. Otolaryngol. Head Neck Surg.* 121:783-789 (1995) ("Werning") and Cincotta et al., *Cancer Res.* 54:1249-1258 (1994) ("Cincotta"), as evidenced by Molitch, *Endocrinol. Metab. Clin. North Am.* 21:(4) (abstract) (1992) ("Molitch").

Claims 1-22 have been rejected as allegedly obvious over the '748 patent in view of Werning and Cincotta as evidenced by Molitch.

The arguments set forth below apply equally to the obviousness-type double patenting rejection and the obviousness rejection. Accordingly, these rejections are traversed together, on the grounds that there is no motivation to combine the '748 patent with Werning and Cincotta to arrive at a method of treating tumors by combining neuroendocrine resetting therapy (NRT) with photodynamic therapy (PDT).

The claims are drawn to treating tumors in a mammal with PDT in combination with NRT using a prolactin enhancer, i.e., administering the prolactin enhancer at appropriate time intervals of day such that the daily plasma prolactin profile of a tumor bearing mammal conforms to or approaches the normal daily plasma prolactin profile for healthy members of the same species and sex of the mammal. The prior art cited by the Examiner discloses treating tumors separately with PDT or NRT, but not in combination. The Examiner's position is that the cited references teach that the combination of photodynamic therapy with administration of a prolactin enhancer results in the increased regression of tumors versus photodynamic therapy alone. Specifically, the Examiner contends that the '748 patent discloses and claims a method for inhibiting neoplasm growth in humans by comparing the prolactin profile of the afflicted human to a standard prolactin profile for healthy humans of the same sex and adjusting the prolactin profile of the afflicted human via administration of a prolactin enhancer, such as melatonin in a certain amount and at certain times. The Examiner also asserts that Werning discloses that the combination of photodynamic therapy with metoclopramide increases the percentage of tumor regression versus photodynamic therapy alone. The Examiner cites Molitch for evidence that metoclopramide is a prolactin

enhancer. According to the Examiner, it would have been obvious to one of ordinary skill in the art to optimize the invention claimed in the '748 patent so as to include PDT.

The Examiner's stated motivation fails, however, because the effect observed in Werning is completely unrelated to metoclopramide's action on prolactin and, more particularly, is completely unrelated to resetting the prolactin rhythm of a tumor bearing mammal. Hence, all discussion in Werning is restricted to metoclopramide and the effects directly attributable to metoclopramide. There is simply no disclosure in Werning that the effect obtained by combining metoclopramide administration and PDT is related in any way to plasma prolactin levels. Prolactin is not mentioned even once in Werning. Hence, Werning suggests that metoclopramide can sensitize tumor cells to chemotherapy and radiation therapy, that metoclopramide has the ability to damage DNA directly and inhibit the repair of DNA damage caused by other agents and that metoclopramide has been reported to increase the distribution of blood flow to tumors. Werning fails to make any suggestion, however, that these effects are mediated through plasma prolactin levels. Accordingly, Werning fails to include any motivation or suggestion that metoclopramide be used to adjust the daily plasma prolactin profile of a tumor bearing mammal, in combination with PDT.

Nor does Molitch's disclosure that metoclopramide is a prolactin enhancer provide an motivation to combine Cincotta with Werning to arrive at the instant claims, in view of Werning's teaching that the prolactin enhancing activity of metoclopramide is not related to the observed enhancement of PDT.

Moreover, Werning, as evidenced by Molitch, teaches away from combining NRT with PDT, as called for in the instant claims. Hence, Werning teaches that there is a direct dose response correlation between the metoclopramide dose and tumor ablation. Doses of 16, 32 and 48 mg/kg, respectively, showed the greatest efficacy in treating tumors, when combined with PDT. Accordingly, Werning teaches that the metoclopramide dose should be maximized to effect treatment in combination with PDT. Adjusting the plasma prolactin profile of a tumor bearing mammal to approach the profile of a normal mammal, however, requires that a prolactin enhancer not be administered to maximize prolactin levels, because maximizing prolactin would not adjust the plasma prolactin profile of a tumor bearing mammal, but would instead lead to uniformly high levels of plasma prolactin, in direct conflict with the teaching of the '748 patent, and in direct

conflict with the instant claims. Hence, the disclosure of Werning teaches away from the disclosure of '748 patent.

Moreover, Werning's incompatibility with the '748 patent is supported by Molitch. Hence, Molitch states that, "Pathologic increases of PRL [prolactin] owing to hypothalamic dysregulation occur with a variety of medications, including...metoclopramide." Accordingly, Molitch does not evidence that metoclopramide, as administered in Werning, is a prolactin enhancer that may be used in combination with '748 patent to arrive at the instant claims. To the contrary, Molitch teaches explicitly that metoclopramide cannot be used to reset the daily plasma prolactin profile of a tumor bearing mammal to approach the profile of a normal mammal. Hence, Molitch and Werning teach away from each of the '748 patent and the instant claims. There is no motivation to combine Werning, as evidenced by Molitch, with the '748 patent to arrive at the instant claims.

For at least the reasons set forth above, none of the prior art cited by the Examiner suggests any motivation or benefit to treating tumors by the combination of adjusting the plasma prolactin profile of a tumor bearing mammal to approach or conform to the profile of a healthy mammal with PDT. For at least this reason, the instant rejections should be withdrawn.

**Unexpected results are obtained with the combination of prolactin resetting therapy and PDT, compared to either therapy alone**

Additionally, the claims are not obvious over the combination of the teachings of the cited references because unexpected results are obtained with the combination of neuroendocrine resetting therapy and PDT, compared to either therapy alone. Examples 1 and 2 and Figure 5 of the application demonstrate the synergistic effects when PDT is combined with NRT using a prolactin enhancer, as called for in the claims. There is no suggestion in the prior art that such synergistic effects could be achieved.

Thus, Example 1, set forth on page 28 of the instant specification, describes an experiment designed to measure the effect of control (C), prolactin (PRL; 20 mcg/mouse at 10 h after light onset at 7 days after tumor inoculation, continuing for 14 days), PDT (D+L; EtNBS photosensitizer; power density of 100J/cm<sup>2</sup> and a total energy of 100J/ cm<sup>2</sup>) and prolactin plus PDT

(D+L+PRL) treatments on tumors in EMT-6 tumor bearing mice. The results of the experiment that are shown in Figure 5 demonstrate the unexpected synergistic effect of the combined treatment.

As shown in Figure 5, the average tumor volume in EMT-6 tumor bearing animals treated with prolactin alone was found to be 56% of the average tumor volume of control animals (i.e., prolactin treatment reduced average tumor volume by 44%). The average tumor volume in EMT-6 tumor bearing animals treated with PDT alone was 43% of the average tumor volume for control animals (i.e., PDT reduced average tumor volume by 57%). Based on these results, therefore, the average tumor volume in EMT-6 tumor bearing animals treated with both prolactin and PDT, obtained by multiplying the results of each individual treatment (i.e.,  $0.56 \times 0.43$ ), is predicted to be 24% of the average tumor volume of control animals (i.e., 76% reduction in the average tumor volume compared to control cells).

The results given in Figure 5 demonstrate, however, that the combined treatment with prolactin and PDT is more effective than the results predicted from the combination of each treatment alone. Hence, the combined treatment actually reduced average tumor volume by 92.4%, compared to control animals, and compared to the predicted value of 76% for the combined treatment. Stated differently, the results showed that the average tumor volume of animals that received the combined treatment was only 7.6% the average tumor volume of control animals. This value is over 3-fold lower than the value of 24% predicted for the combined treatment, based on the results of the individual treatments. Hence, the combined treatment with PDT and prolactin lead to an unexpectedly greater reduction in tumor volume than that predicted from the results obtained with each treatment alone. The results of Example 1 are therefore objective evidence of the remarkable results achieved by the combined treatment over either treatment alone.

Further experimental evidence of the synergy obtained in treating tumors with a prolactin enhancer and PDT is set forth in Example 2 (see specification at pages 28-29). Example 2 reports that, when PDT with the benzophenothiazine photosensitizer EtNBS is used alone, at a power density of 50 mW/cm<sup>2</sup> and a total energy of 180 J, tumor "cure" (tumor-free for at least 90 days) of 4-8 mm diameter tumors can be achieved in 70-100% of the cases, and is largely dependent upon the tumor size at the time of PDT. In contrast, if intraperitoneal prolactin is administered (20 mcg/mouse/day at 10 h after light onset, starting from day of tumor cell inoculation) in conjunction

with PDT, then the cure rate is 100%. Furthermore, the time course of tumor eradication is significantly faster with the combined treatment versus PDT alone. Hence, tumors remained noticeable 48-72 h following PDT treatment alone, taking 14 days to regress completely, with eschar formation at 24-48 hours. In contrast, when timed administration of prolactin was combined with PDT, 100% of the treated animals exhibited eschar formation and complete tumor eradication within 24 h of PDT. Hence, in Example 2, the combination of neuroendocrine resetting therapy and PDT lead to more rapid tumor eradication and a higher tumor eradication rate (i.e., 100%), compared to PDT alone.

Moreover, the timing of prolactin administration is essential in order to obtain the synergistic effect of PDT and prolactin treatment. The specification makes it clear that prolactin should be administered during the time of the plasma prolactin peak in a healthy mammal of the same sex.

**V. Rejection for Obviousness-Type Double Patenting over the '914 Patent in view of *Lin* and *Cincotta***

Claims 1-4, 10, 15, 20 and 21 have been rejected for obviousness-type double patenting over claims 12, 13, 28 and 30 of *Cincotta et al.*, U.S. Patent No. 6,071,914 ("the '914 patent"), in view of *Lin, Cancer Cells*, 1991, 3:4.

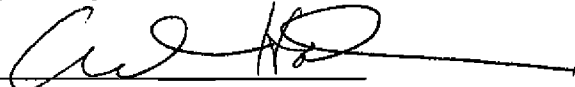
For the reasons identical to those set forth above in Section IV the claims are not obvious over the combination of the teachings of the '914 patent and *Cincotta*, because unexpected results are obtained with the combination of NRT and PDT, compared to either therapy alone.

## **VI. Conclusion**

For the reasons set forth above, applicants respectfully request withdrawal of the nonstatutory double patenting rejections and the rejection for obviousness under 35 U.S.C. § 103.

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Respectfully submitted,

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